

X-12799

9/
-/-

We Claim:

1. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:
 - a) replacing tryptophan at position 53 with aspartic acid;
 - b) replacing threonine at position 88 with proline;
 - c) replacing alanine at position 107 with serine, aspartic acid, glutamic acid or threonine;
 - d) replacing isoleucine at position 110 with threonine or glutamic acid; or
 - e) replacing proline at position 104 with serine, and physiologically acceptable salts of said polypeptide and said fragment.
2. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:
 - a) replacing alanine at position 2 or position 12 with asparagine;
 - b) replacing proline at position 25, position 38, position 126 or position 171 with asparagine;
 - c) replacing arginine at position 35 with asparagine;
 - d) replacing serine at position 37 with asparagine and proline at position 38 with any other naturally occurring amino acid;
 - e) replacing serine at position 166 with asparagine;
 - f) replacing leucine at position 172 with asparagine;
 - g) replacing aspartic acid at position 194 with asparagine; or
 - h) replacing threonine at position 114 with asparagine and proline at position 115 with any naturally occurring amino acid;

AMENDED SHEET

X-12799

92-

and physiologically acceptable salts of said polypeptide and said fragment.

3. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

- a) replacing asparagine at position 63 with tryptophan;
- b) replacing glycine at position 67 with aspartic acid and alanine at position 94 or glycine at position 95 with tyrosine;
- c) replacing arginine at position 69 with glutamic acid;
- d) replacing arginine at position 82 with glutamic acid or threonine;
- e) replacing alanine at position 94 with tryosine and glycine at position 95 with aspartic acid;
- f) replacing phenylalanine at position 96 with glutamine;
- g) replacing alanine at position 101 with threonine; or
- h) replacing glycine at position 95 with aspartic acid;

and physiologically acceptable salts of said polypeptide and said fragment.

4. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

- a) replacing arginine at position 10 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then alanine at position 12 is optionally replaced with serine or threonine;
- b) replacing glutamic acid at position 13 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then glycine at position 15 is optionally replaced with serine or threonine;

X-12799

93-

- c) replacing glutamic acid at position 16 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then leucine at position 18 is optionally replaced with serine or threonine;
- d) replacing arginine at position 17 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then valine at position 19 is optionally replaced with serine or threonine;
- e) replacing arginine at position 31 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then cysteine at position 33 is optionally replaced with serine or threonine;
- f) replacing arginine at position 34 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then aspartic acid at position 36 is optionally replaced with serine or threonine;
- g) replacing arginine at position 35 with glutamine, asparagine, serine or threonine;
- h) replacing aspartic acid at position 36 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then proline at position 38 is optionally replaced with serine or threonine;
- i) replacing arginine at position 143 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then cysteine at position 145 is optionally replaced with serine or threonine; or
- j) replacing aspartic acid at position 161 with glutamine, asparagine, serine or threonine, provided that when the replacing amino acid is asparagine, then leucine at position 163 is optionally replaced with serine or threonine,

AMENDED SHEET

X-12799

94-

and physiologically acceptable salts of said polypeptide and said fragment.

5. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

- a) replacing alanine at position 2, 12, 107, 179 or 209 with threonine;
- b) replacing threonine at position 4 or 162 with alanine;
- c) replacing valine at position 1 or isoleucine at position 110 with methionine;
- d) replacing glutamic acid at position 13 with aspartic acid;
- e) replacing arganine at position 17 with tryptophan;
- f) replacing alanine at position 75 with proline;
- g) replacing serine at position 102 with leucine;
- h) replacing glycine at position 169 with alanine;
- i) replacing glutamic acid at position 183 with lysine;
- j) replacing glutamine at position 225 with arginine;
- k) replacing glycine at position 237 with glutamic acid; or
- l) replacing valine at position 270 with glycine,

and physiologically acceptable salts of said polypeptide and said fragment.

6. A FLINT analog comprising a polypeptide having FLINT biological activity, said polypeptide having the amino acid sequence of SEQ ID NO:1 modified by:

- a) replacing alanine at position 12 with asparagine and optionally replacing glutamic acid at position 13 with glutamine;
- b) replacing arginine at position 34 with asparagine and replacing aspartic acid at position 36 with threonine;
- c) replacing arginine at position 35 with asparagine and optionally replacing serine at position 37 with threonine;

AMENDED SHEET

X-12799

95-

- d) replacing serine at position 132 with asparagine and optionally replacing serine at position 134 with threonine;
- e) replacing aspartic acid at position 194 with asparagine and optionally replacing serine at position 196 with threonine;
- f) replacing arginine at position 35 and aspartic acid at position 194 with asparagine;
- g) replacing alanine at position 12 with asparagine, optionally replacing glutamic acid at position 13 with glutamine, replacing aspartic acid at position 194 with asparagine and optionally replacing serine at position 196 with threonine;
- h) replacing arginine at position 34 with asparagine, replacing aspartic acid at position 36 with threonine, replacing aspartic acid at position 194 with asparagine and optionally replacing serine at position 196 with threonine;
- i) replacing arginine at position 35 and aspartic acid at position 194 with asparagine and replacing serine at position 37 and/or position 196 with threonine; or
- j) replacing arginine at position 218 with glutamine,

and physiologically acceptable salts of said polypeptide and said fragment.

Sub A 17

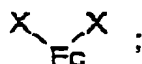
7. A fragment of a FLINT analog of claims 1 through 6 wherein said fragment is defined by residues 1 through 218 of SEQ ID NO:1.

8. A FLINT analog defined by residues 1 through 218 of SEQ ID NO:1.

9. A FLINT analog defined by residues 1 through 216 of SEQ ID NO:1.

10. A fusion protein represented by the following structural formula:

wherein:



AMENDED SHEET

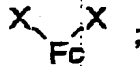
X-12799

96-

Fc is an Fc fragment of an antibody;
 each X is independently the peptide derivative of Claim 1, 2, 3, 4, 5,
 6, 7, 10, 11, or 12; and
 each polypeptide represented by X is covalently linked at its C-terminus to the N-terminus of one of the polypeptides which form the Fc fragment of the antibody.

11. A fusion protein represented by the following structural formula:

wherein:



Fc is an Fc fragment of an antibody;
 each X is a protease-resistant FLINT analog; and
 each polypeptide represented by X is covalently linked at its C-terminus to the N-terminus of one of the polypeptides which form the Fc fragment of the antibody.

12. A protein of Claim 10 wherein Fc is an Fc fragment from a human antibody.

Sub A2 13. A protein of Claim 11 wherein Fc is an Fc fragment from a human antibody

14. The protein of Claims 12 or 13 wherein Fc lacks the hinge region.

15. A protein of claim 11 wherein said analog comprises SEQ ID NO:1 and wherein arginine at position 218 is replaced by glutamine.

16. A protein of claim 11 said analog comprising the amino acid sequence of SEQ ID NO:1 wherein Arg at position 218 is replaced by an amino acid selected from the group consisting of:

a. any naturally occurring amino acid that is not Arg;

AMENDED SHEET

X-12799

97-

- b. any positively charged amino acid that is not Arg;
- c. any negatively charged amino acid that is not Arg;
- d. any polar uncharged amino acid that is not Arg;
- e. any non-polar amino acid that is not Arg; and
- f. any amino acid that is Glu, Gln, Ala, Asn, Gly, Ser, Val, or Tyr.

17. A nucleic acid that encodes any one of the FLINT analogs of claims 1 through 16.

18. A vector comprising a nucleic acid of claim 17.

19. Use of a FLINT analog of claims 1 through 16 in the preparation of a medicament useful in treating a disease or disorder selected from the group consisting of acute lung injury, acute respiratory distress syndrome, pulmonary fibrosis, chronic obstructive pulmonary disease, ulcerative colitis, or Crohn's disease.

20. A pharmaceutical composition comprising a FLINT analog of claims 1 through 16 together with one or more pharmaceutically acceptable diluents, carriers or excipients therefor.